

WHAT IS CLAIMED IS:

1. A chemically defined, structurally homogeneous conjugate of formula A-L-P, in which:

A represents a glycosylated peptide that binds to a cell-surface receptor on a cell of which the liver is comprised,

L represents a bifunctional linker, which does not comprise a naturally occurring amino acid and which is covalently bonded to A and P in a regiospecific manner, and

P represents a monomer, homopolymer or heteropolymer comprising at least one nucleotide or an analogue thereof, wherein said nucleotide or analogue thereof inhibits the intracellular biosynthesis of nucleotides or nucleic acids in a sequence-independent manner,

wherein either or both of the covalent bond between A and L and the covalent bond between L and P can be cleaved intracellularly.

2. The conjugate of claim 1, wherein the nucleotide or analogue thereof comprises an aglycone-modified nucleoside analogue.

3. The conjugate of claim 2, wherein the aglycone-modified nucleoside analogue is 5-fluoro-2'-deoxyuridine (5FdU).

4. The conjugate of claim 2, wherein the aglycone-modified nucleoside analogue comprises a fluorinated pyrimidine.

5. The conjugate of claim 4, wherein the fluorinated pyrimidine is 5-fluorouracil (5FU).

6. The conjugate of claim 3, wherein P is a homopolymer of 5FdU.

7. The conjugate of claim 6, wherein the homopolymer contains 2 to 12 5FdU.
8. The conjugate of claim 7, wherein each of the 2 to 12 5FdU is covalently bonded to each adjacent 5FdU by a phosphodiester bond or a phosphothioate bond.
9. The conjugate of claim 6, wherein the homopolymer contains 2 to 6 5FdU.
10. The conjugate of claim 9, wherein each of the 2 to 6 5FdU is covalently bonded to each adjacent 5FdU by a phosphodiester bond or a phosphothioate bond.
11. The conjugate of claim 3, wherein P is a monomer.
12. The conjugate of claim 2, wherein the aglycone-modified nucleoside analogue is an azapyrimidine nucleoside.
13. The conjugate of claim 12, wherein the azapyrimidine nucleoside is 5-azacytidine (5-AzaCyd), 5-azauridine (5-AzaUrd), 6-azacytidine (6-AzaCyd), or 6-azauridine (6-AzaUrd).
14. The conjugate of claim 12, wherein the aglycone-modified nucleoside analogue is a 3-deazapyrimidine nucleoside.
15. The conjugate of claim 14, wherein the 3-deazapyrimidine nucleoside is 3-deazauridine (3-DeazaUrd).
16. The conjugate of claim 1, wherein the nucleotide or analogue thereof comprises a sugar-modified nucleoside.

17. The conjugate of claim 16, wherein the sugar-modified nucleoside is 1- β -D-arabinofuranosyl-cytosine (AraC), cyclocytidine, 2'-O-nitro-AraC, 9- β -D-arabinofuranosyl-adenine (araA), cyclaridine, 2', 2'-difluorodeoxycytidine, 2'-deoxy-2'-methylidenecytidine (DMDC) or an acyclonucleoside.

18. The conjugate of claim 17, wherein the acyclonucleoside is acyclovir or gancyclovir.

19. The conjugate of claim 1, wherein the nucleotide or analogue thereof comprises fludarabine phosphate, 2-halo-adenine-2'-deoxyribonucleoside, 2-chloroadenine-arabinonucleoside, 2'-deoxycoformycin, or 2-halo-2'-fluoroarabinonucleoside.

20. The conjugate of claim 1, wherein, when P comprises more than one nucleotide or analogue thereof, the nucleotides or analogs thereof are covalently bonded to each other and at least one of the covalent bonds can be cleaved intracellularly.

21. The conjugate of claim 1, wherein P comprises a radioactive nuclide.

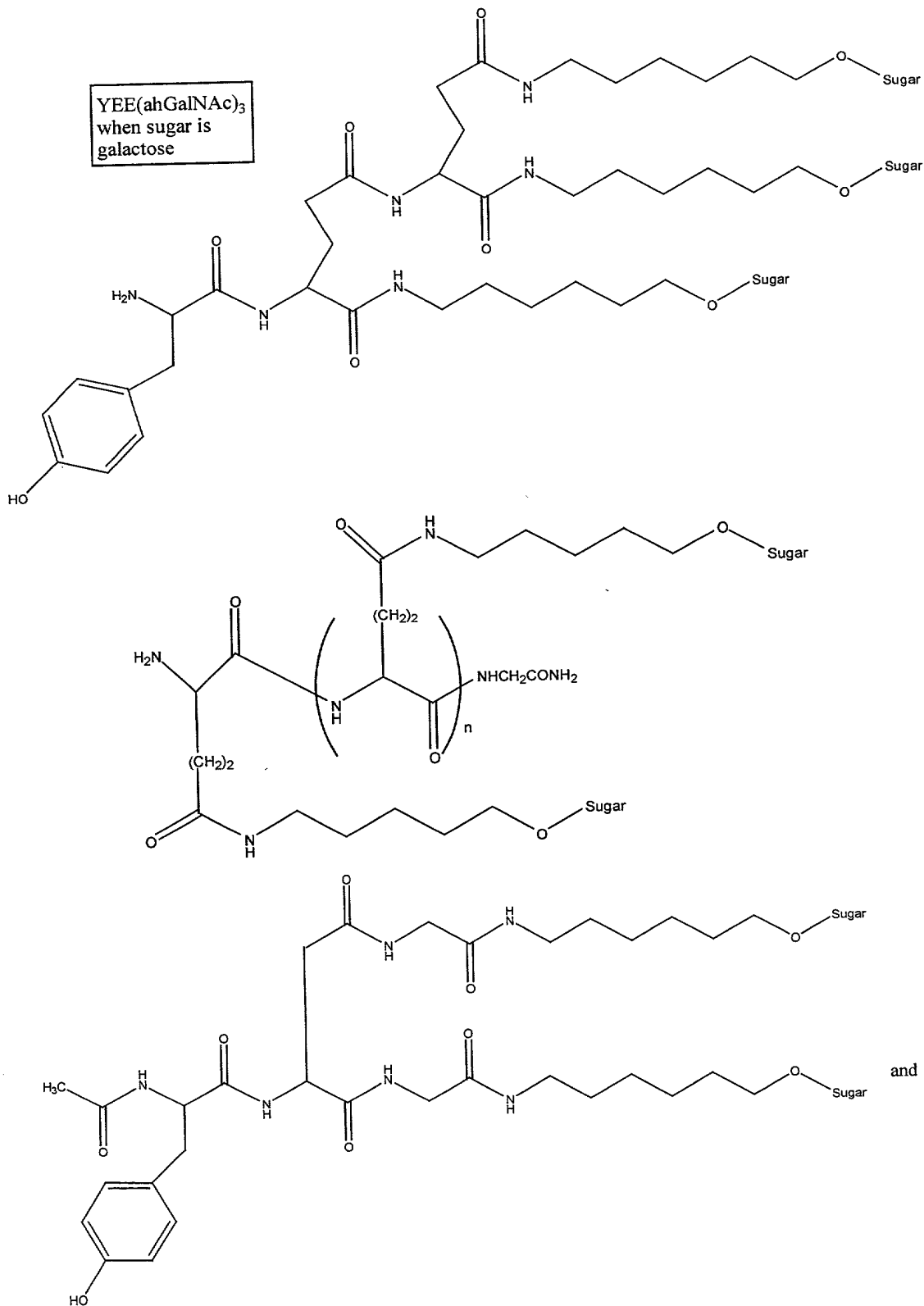
22. The conjugate of claim 1, wherein A is covalently bonded to L through an amide bond.

23. The conjugate of claim 1, wherein L is covalently bonded to P through a thioether bond.

24. The conjugate of claim 1, wherein A is selected from the group consisting of

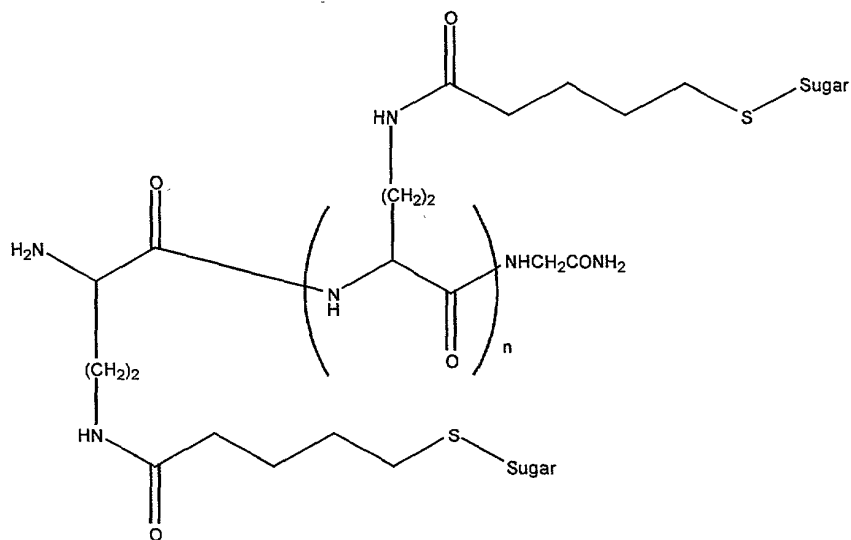
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YEE(ahGalNAc)₃
when sugar is
galactose



and

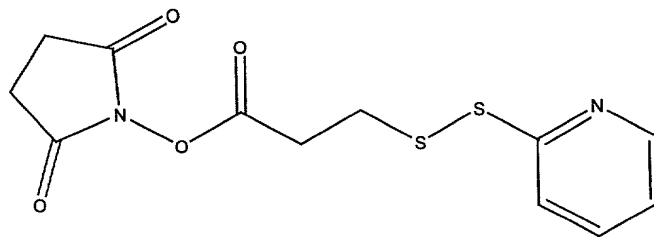
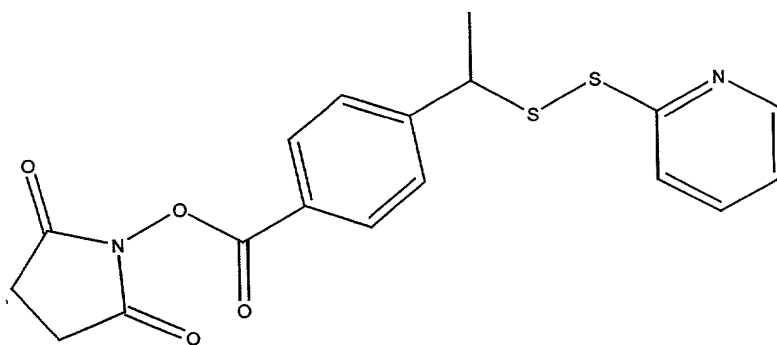
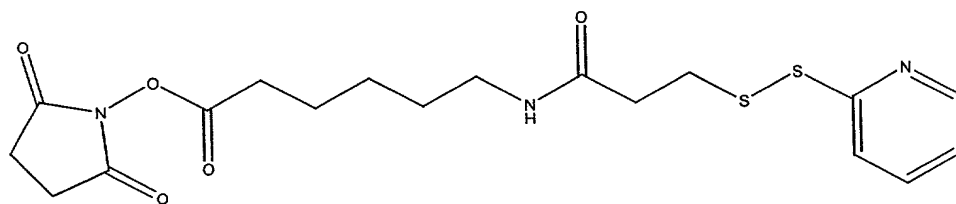
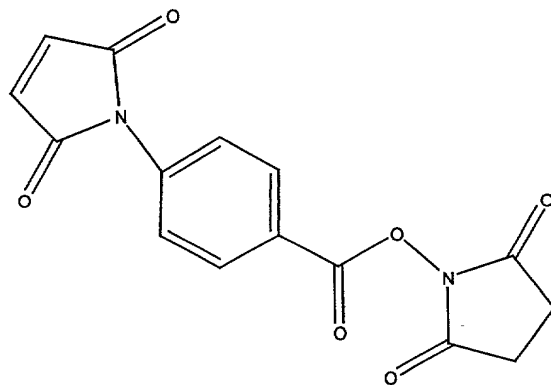
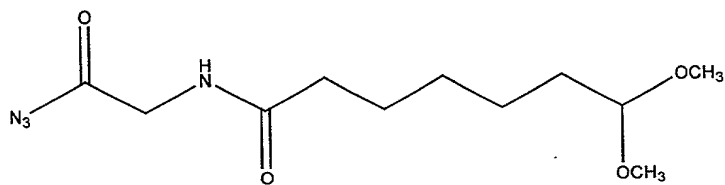
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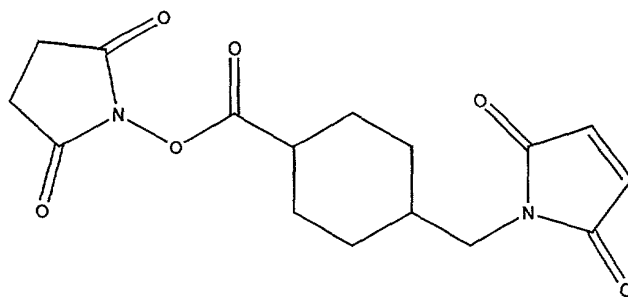


wherein the sugar is glucose, N-acetylglucosamine, galactose, N-acetylgalactosamine, mannose or fucose.

25. The conjugate of claim 1, wherein A is YEE(ahGalNAc)₃.
26. The conjugate of claim 1, wherein L is a product of SMCC (N-hydroxysuccinimidyl 4-(N-methylmaleimido)cyclohexyl-1-carboxylate).
27. The conjugate of claim 10, wherein A is YEE(ahGalNAc)₃.
28. The conjugate of claim 27, wherein L is a product of SMCC.
29. The conjugate of claim 1, wherein L is heterobifunctional.
30. The conjugate of claim 1, wherein L is a product of a cross-linking reagent selected from the group consisting of

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and α -citraconyl-K-(ϵ -FMOC)PILFFRL (N- α -citraconyl-Lys(ϵ FMOC)-Pro-Ile-Leu-Phe-Phe-Arg-Lys-COOH).

31. A chemically defined, structurally homogeneous conjugate of formula A-L-P, in which:

A represents a galactosylated peptide that binds to a cell-surface asialoglycoprotein receptor on a cell,

L represents a bifunctional linker, which does not comprise a naturally occurring amino acid and which is covalently bonded to A and P in a regiospecific manner, and

P represents a monomer, homopolymer or heteropolymer comprising at least one nucleotide or an analogue thereof, wherein said nucleotide or analogue thereof inhibits the intracellular biosynthesis of nucleotides or nucleic acids in a sequence-independent manner,

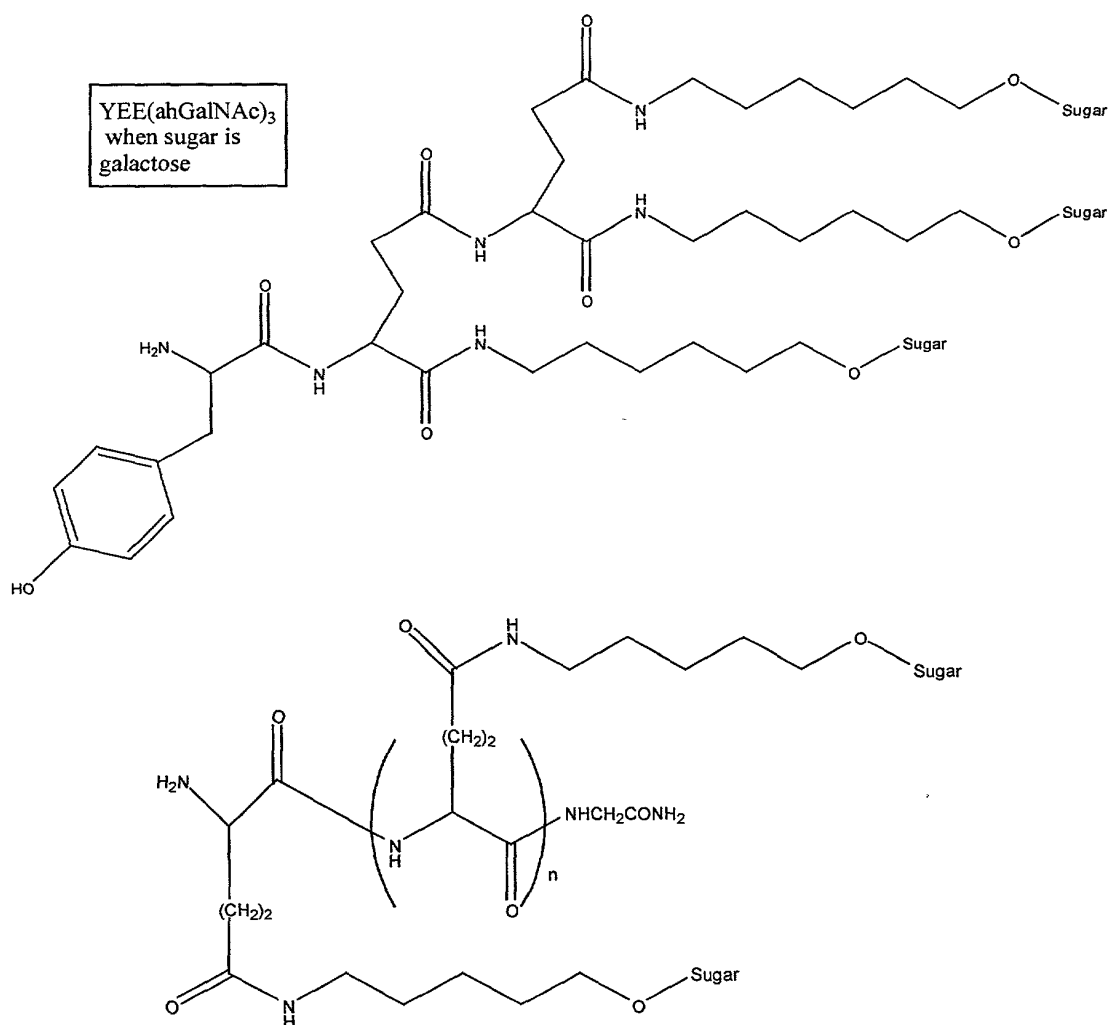
wherein either or both of the covalent bond between A and L and the covalent bond between L and P can be cleaved intracellularly.

32. The conjugate of claim 31, wherein the nucleotide or analogue thereof comprises an aglycone-modified nucleoside analogue.

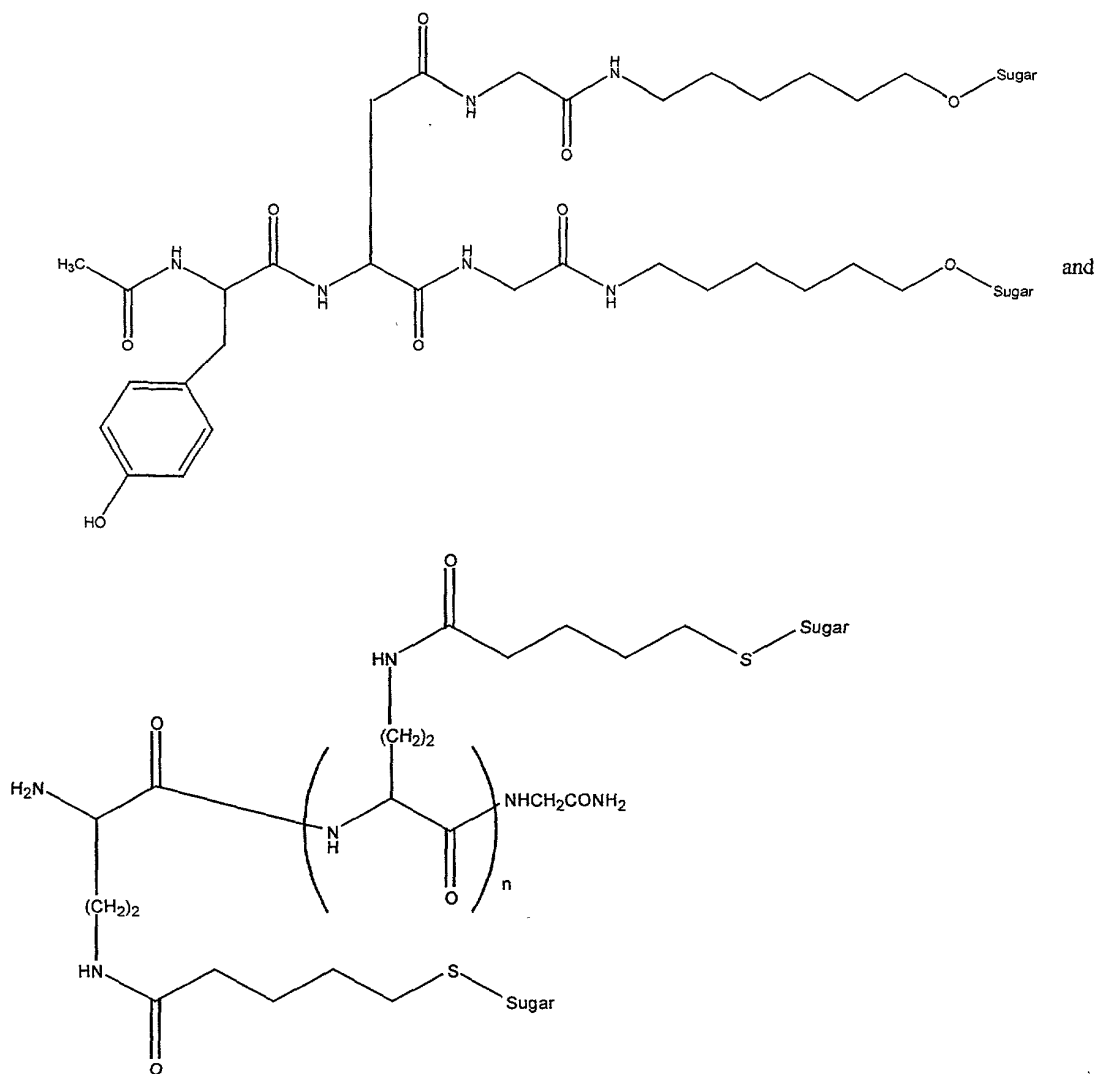
33. The conjugate of claim 32, wherein the aglycone-modified nucleoside analogue is 5FdU.

34. The conjugate of claim 32, wherein the aglycone-modified nucleoside analogue comprises a fluorinated pyrimidine.
35. The conjugate of claim 34, wherein the fluorinated pyrimidine is 5FU.
36. The conjugate of claim 33, wherein P is a homopolymer of 5FdU.
37. The conjugate of claim 36, wherein the homopolymer contains 2 to 12 5FdU.
38. The conjugate of claim 37, wherein each of the 2 to 12 5FdU is covalently bonded to each adjacent 5FdU by a phosphodiester bond or a phosphothioate bond.
39. The conjugate of claim 36, wherein the homopolymer contains 2 to 6 5FdU.
40. The conjugate of claim 39, wherein each of the 2 to 6 5FdU is covalently bonded to each adjacent 5FdU by a phosphodiester bond or a phosphothioate bond.
41. The conjugate of claim 33, wherein P is a monomer.
42. The conjugate of claim 31, wherein, when P comprises more than one nucleotide or analogue thereof, the nucleotides or analogs thereof are covalently bonded to each other and at least one of the covalent bonds can be cleaved intracellularly.
43. The conjugate of claim 31, wherein P comprises a radioactive nuclide.

44. The conjugate of claim 31, wherein A is covalently bonded to L through an amide bond.
45. The conjugate of claim 31, wherein L is covalently bonded to P through a thioether bond.
46. The conjugate of claim 31, wherein A is selected from the group consisting of



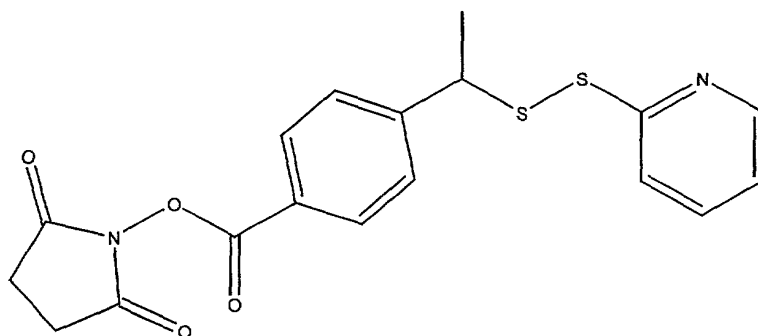
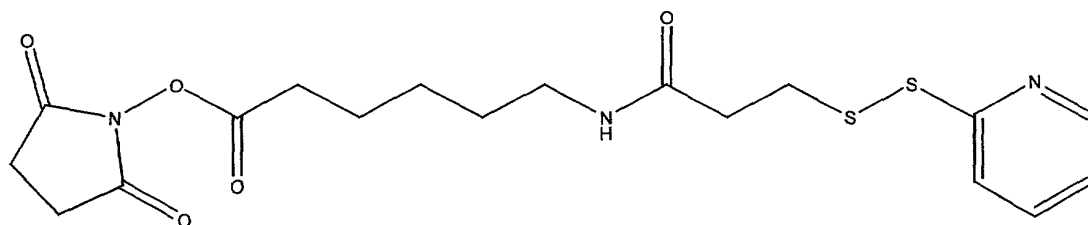
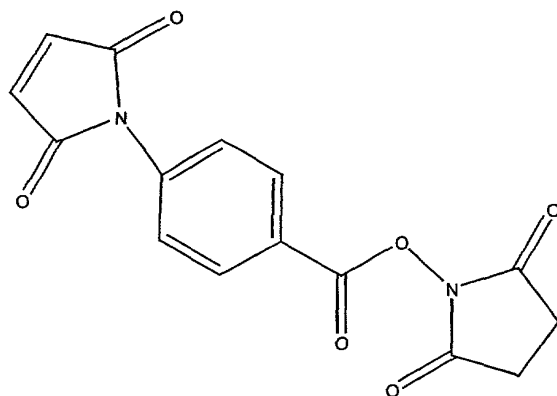
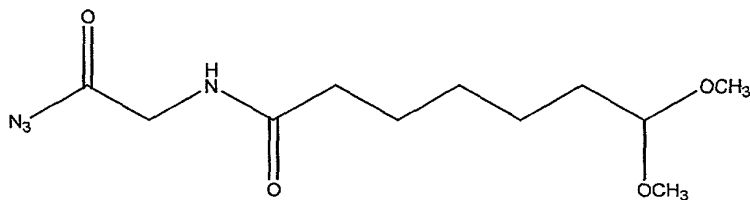
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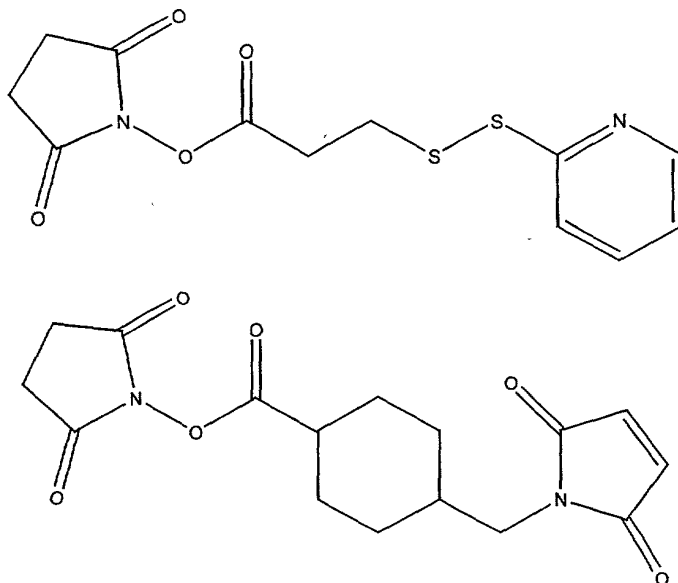
wherein the sugar is glucose, N-acetylglucosamine, galactose, N-acetylgalactosamine, mannose or fucose.

47. The conjugate of claim 31, wherein A is YEE(ahGalNAc)₃.
48. The conjugate of claim 31, wherein L is a product of SMCC.
49. The conjugate of claim 31, wherein L is heterobifunctional.

50. The conjugate of claim 31, wherein L is a product of a cross-linking reagent selected from the group consisting of



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and α -citraconyl-K-(ϵ -Fmoc)PILFFRL.

51. A composition comprising a conjugate of claim 1.
52. The composition of claim 51, which comprises a pharmaceutically acceptable carrier.
53. A composition comprising a conjugate of claim 31.
54. The composition of claim 53, which comprises a pharmaceutically acceptable carrier.
55. A method of inhibiting abnormal cellular proliferation in a mammal in need thereof, which method comprises administering to the mammal an abnormal cellular proliferation-inhibiting amount of a conjugate of claim 1 or a composition comprising same, whereupon the abnormal cellular proliferation in the mammal is inhibited.

56. The method of claim 55, wherein the abnormal cellular proliferation is hepatocellular carcinoma.

57. A method of inhibiting abnormal cellular proliferation in a mammal in need thereof, which method comprises administering to the mammal an abnormal cellular proliferation-inhibiting amount of a conjugate of claim 31 or a composition comprising same, whereupon the abnormal cellular proliferation in the mammal is inhibited.

58. The method of claim 57, wherein the abnormal cellular proliferation is hepatocellular carcinoma.

59. A method of inhibiting replication of a virus in a mammal in need thereof, which method comprises administering to the mammal a viral replication-inhibiting amount of a conjugate of claim 1 or a composition comprising same, whereupon the replication of a virus in the mammal is inhibited.

60. The method of claim 59, wherein the virus is hepatitis.

61. A method of inhibiting replication of a virus in a mammal in need thereof, which method comprises administering to the mammal a viral replication-inhibiting amount of a conjugate of claim 31 or a composition comprising same, whereupon the replication of a virus in the mammal is inhibited.

62. The method of claim 61, wherein the virus is hepatitis.